The Australasian Resuscitation In Sepsis Evaluation: FLUid or vasopressors In Emergency Department Sepsis, a multicentre observational study (ARISE FLUIDS observational study): Rationale, methods and analysis plan

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The **A**ustralasian **R**esuscitation **I**n **S**epsis **E**valuation: **FLU**id or Vasopressors **I**n Emergency **D**epartment **S**epsis, a multi-centre observational study (ARISE FLUIDS observational study): rationale, methods and analysis plan

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ABSTRACT

Objectives: There is uncertainty about the optimal intravenous (IV) fluid volume and timing of vasopressor commencement in the resuscitation of patients with sepsis and hypotension. We aim to study current resuscitation practices in emergency departments (EDs) in Australia and New Zealand (ARISE FLUIDS observational study).

Methods/ Design: ARISE FLUIDS is a prospective, multicentre observational study in 74 hospitals in Australia and New Zealand. It will include adult patients presenting to the ED during a 30-day period with suspected sepsis and hypotension (SBP<100mmHg) despite at least 1000ml fluid resuscitation. We will obtain data on baseline demographics, clinical and laboratory variables, all IV fluid given in the first 24 hours, vasopressor use, time to antimicrobial administration, admission to intensive care, organ failure and in-hospital mortality. We will specifically describe: 1) the volume of fluid administered at the following time points: when meeting eligibility criteria, in the first 6 hours, at 24 hours and prior to vasopressor commencement, and; 2) the frequency and timing of vasopressor use in the first 6 hrs and at 24hrs. Screening logs will provide reliable estimates of the proportion of ED patients meeting eligibility criteria for a subsequent randomised controlled trial (RCT).

Discussion: This multicentre, observational study will provide insight into current haemodynamic resuscitation practices in patients with sepsis and hypotension as well as estimates of practice variation and patient outcomes. The results will inform the design and feasibility of a multicentre Phase III trial of early haemodynamic resuscitation in patients presenting to ED with sepsis and hypotension.

Key words: emergency department, fluid therapy, hypotension, sepsis, vasopressors

INTRODUCTION

Fluid volume in resuscitation was identified as the top priority in sepsis research in a recent editorial authored by leading sepsis experts.[1] It also features prominently among the top research priorities identified by emergency physicians in the United Kingdom, Australia and New Zealand.[2,3]

The amount of fluid given in sepsis has changed over the last two decades. Early goal directed therapy (EGDT) decreased sepsis mortality in emergency department (ED) patients in a small, single-centre study in the United States published in 2001.[4] EGDT consists of a protocolised bundle of care that includes liberal intravenous (IV) fluid resuscitation, vasoactive therapy, central venous oxygen saturation monitoring and red blood cell transfusion. Subsequent large-scale multicentre EGDT trials[5-7] conducted between 2007 and 2014 showed that although timing of fluid administration was varied, the total of fluid administered between ED presentation and 6 hours post randomisation was similar in the usual care and EGDT arms, with no difference in mortality. These studies suggest that IV fluid resuscitation has been adopted into usual practice as part of a 'bundle of care', and that this bundled care may be associated with falling sepsis mortality.[8] However, it remains unclear which bundle elements (changes in resuscitation practices, early sepsis recognition, more timely and appropriate broad-spectrum antibiotics) are primarily responsible for the observed reduction in mortality. Despite such lack of evidence from clinical trials, the surviving sepsis campaign (SSC) guidelines recommend an initial 30ml/kg of IV isotonic crystalloid for patients with sepsis and hypoperfusion.[9]

In contrast to this SSC recommendation, observational data and recent randomised trials suggest there may be potential harm associated with the liberal use of fluids in sepsis.[10-15] A preclinical study supports the finding from these trials that IV fluid can worsen shock, as it showed that sheep with endotoxemic shock receiving an IV fluid bolus had an increased requirement for vasopressors.[16] The seminal FEAST study showed increased mortality in African children with sepsis who received fluid bolus resuscitation compared to no fluid bolus.[12] A small study in adults in Zambia also showed higher mortality with

larger amounts of fluid administered as part of protocolised sepsis care.[14] However, such evidence cannot be reliably extrapolated to adults presenting to the ED with sepsis in high-income countries such as Australia and New Zealand.

The role of liberal compared with restricted volume fluid resuscitation as first-line treatment for sepsis-related hypotension represents a significant knowledge gap, with uncertainty about the optimal volume, rate of administration and type of fluid, as well as the timing, route of administration and preferred agent for vasopressor support.

We conducted a phase II clinical feasibility trial which compared a restricted fluid protocol and early initiation of vasopressor support with standard care.[17] Our study found that the restricted fluid and early vasopressor regimen resulted in a significantly lower volume of fluid administered over the first 24 hours of care, with no signal of harm. A lower volume of fluid was administered in the usual care arm than in the ARISE study[7] (3.0 vs 4.2L – pre-randomisation fluids up to 6 hours post-randomisation).

Accordingly, the ARISE FLUIDS observational study aims to provide further insights regarding the incidence of sepsis with hypotension in Australian and New Zealand EDs and current clinical practice regarding the use of IV fluids and vasopressors in sepsis resuscitation including variations in care, and test screening and recruitment procedures for a future Phase III trial.

The study aims of ARISE FLUIDS are to:

1. Describe current practice regarding IV fluid administration and vasopressor use
2. Determine in-hospital mortality, and the receipt of organ support
3. Determine the incidence of patients being managed in ED with sepsis and hypotension

METHODS AND ANALYSIS PLAN

Design and setting

A prospective, multicentre observational study in the EDs of 74 metropolitan, regional and rural hospitals in Australia and New Zealand. The ARISE FLUIDS study conforms to the STROBE principles for design and reporting of observational studies.[18] The ARISE FLUIDS study has been endorsed by the Australasian College for Emergency Medicine Clinical Trials Network (ACEM CTN) and hospital participation will be by an expression of interest process through the ACEM CTN. Interested sites will identify a local investigator who is responsible for the conduct of the project. The ARISE FLUIDS co-ordinating centres are the Gold Coast University Hospital (GCUH), the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), the Centre for Centre for Clinical Research in Emergency Medicine (CCREM) and the Medical Research Institute of New Zealand (MRINZ), with oversight from a steering committee comprised of both emergency physicians and intensive care physicians representing all geographical areas. Human Research and Ethics (HREC) approval has been obtained for all sites according to local requirements. All regions approved data collection without requiring patient consent.

Participants

Adult patients (age ≥18 years) presenting to the ED and meeting all of the inclusion criteria and none of the exclusion criteria at any time during their ED stay will be eligible for enrolment into the study.

Inclusion criteria:

1. Clinically suspected infection
2. IV antimicrobials commenced
3. Systolic blood pressure (SBP) <100 mm Hg at any point despite at least 1000ml IV fluid resuscitation, given as fluid bolus(es) of at least 500ml, within 60 minutes per bolus, inclusive of pre-hospital fluids.

Exclusion criteria:

1. Hypotension suspected to be due to another cause e.g. arrhythmia, haemorrhage
2. Confirmed or suspected pregnancy
3. Comorbidities such that ICU admission for vasopressor use is not appropriate
4. Death deemed imminent or inevitable
5. Life expectancy <90 days
6. Transfer from another acute care hospital

Eligible patients will be identified during a consecutive 30-day period between 13 September 2018 and 31 December 2018.

Screening, data collection and follow-up

Potentially eligible patients will be screened prospectively using a preformatted screening form (appendix A). All sites will receive standardised education material to optimise screening. Screening triggers will be the collection of blood cultures, administration of IV antimicrobials and/or hypotension. Sites with existing sepsis pathways can add the ARISE FLUIDS screening form to the pathway. Patients will be monitored for development of the inclusion criteria throughout their ED stay. A final determination regarding eligibility will be made on departure from the ED. The screening form will be completed for all screened patients with data collected in the screening log. For enrolled patients, additional data will be collected on a case report form (CRF) by local investigators. This CRF will include data collected at 6 and 24 hours post-enrolment as well as clinical outcome variables up to hospital discharge as detailed in the outcomes section below and in Appendix B. The hardcopy CRF will remain on site for audit purposes, and data will be entered in a de-identified format into a purpose-built web-based database management system (REDCap®) hosted by the ANZIC-RC, Monash University.

Outcomes

Baseline characteristics and comorbidities

Participating sites will provide the number of all adult ED presentations for the study period. Baseline data collected at enrolment are summarised in Table 1 and include patient demographics and co-morbidities, vital signs, serum lactate and the total amount of IV fluid administered prior to enrolment (including pre-hospital IV fluids).

Data at 6 and 24 hours and hospital discharge

The CRF includes data at 6 and 24 hours post-enrolment for vital signs, blood gas analyses, receipt of invasive ventilation and laboratory data. The volume and type of IV fluids and the type and timing of vasopressor administration in the first 24 hours post-recruitment are recorded. All participants will be followed to hospital discharge. Follow-up data will include processes of care and clinical outcomes as outlined below and in Table 2.

Fluids

We will report total cumulative fluid volume administered up to 24 hours post-recruitment. This will include volumes prior to recruitment, as well as at 6 and 24 hours (including pre-hospital fluids) after recruitment. We will record the volume of each type of fluid (crystalloid, colloid, blood products, albumin) administered as resuscitation therapy. Intravenous flushes and fluid administered as a drug diluent (e.g. antimicrobials) will not be included.

Vasopressors

We will report the number of participants who have a vasopressor infusion administered for at least one hour up to 24 hours post-recruitment. The number of patients in whom vasopressors are commenced in the ED will be recorded. We will report the volume of IV fluid prior to first commencing a vasopressor and the time from ED presentation to commencement. Furthermore, we will report the time to insertion of a central venous

catheter (CVC) or peripherally inserted central catheter (PICC). Reported vasopressor drugs will include noradrenaline, metaraminol, adrenaline, dopamine, phenylephrine and vasopressin. We will also record episodes of use of inotropic agents (e.g. dobutamine). The total duration of each infusion from commencement to cessation will be recorded. If a vasopressor infusion is restarted within 24 hours of cessation, this will be considered the same episode. The aggregate total of all time periods requiring vasoactive medication for each patient will be reported

Time to antibiotics

Time to commencement of the first antimicrobial administered in the ED will be reported and measured from the time of ED triage.

Clinical outcomes

We will report the source of ED sepsis (hospital discharge diagnosis), ED length of stay and disposition, destination at hospital discharge and in-hospital mortality. For those patients transferred from the ED to ICU, ICU duration of stay, receipt and duration of invasive ventilation, vasopressors and acute renal replacement therapy and ICU mortality are collected.

Screening and enrolment

We will report the number of patients presenting to the ED with sepsis and hypotension and report the enrolment rate (number recruited divided by the number screened). The number of recruited patients, together with the adult attendance to the ED during the same 30-day period, will provide eligibility estimates for recruitment into a Phase III trial.

Analysis

This study is observational in nature and the outcome analyses will be descriptive. There will be no imputation of missing values.

Trial profile

The screening and recruitment process and flow of participants through the study will be reported as outlined in Figure 1.

Primary analysis

We will perform descriptive analysis of the baseline variables, primary process-of-care measures and clinical outcome variables (e.g. fluid volume administered at eligibility, at 6 and 24 hours and prior to vasopressor commencement as well as frequency, timing and duration of vasopressor use, ED disposition, ICU admission, invasive organ support and in-hospital mortality), by reporting measures of central tendency and distribution (mean +/-standard deviation; median +/- interquartile range), and proportions (%), as appropriate. Interquartile ranges and 95% confidence intervals will be reported as appropriate.

Clinical outcomes (ICU admission, mortality, receipt and duration of organ support) will be compared according to (quartiles of) volume of fluid administered up to 6 hours post-recruitment as well as the use of, and time to, vasopressor infusion in quartiles post-recruitment and post-ED presentation.

We will study the strength of the association between process-of-care measures and outcome variables, both in crude and adjusted analyses. Univariate comparison of proportions (where appropriate) will be by Chi square or Fisher's exact test, comparison of continuous data will utilise a Student's t-test or Mann-Whitney U test, as appropriate. To identify predictors of outcome and potential heterogeneity between sites, multivariable regression will be performed adjusting for the pre-defined baseline

covariates of age, APACHE II score, blood lactate concentration, and site, with the latter treated as a random effect.

Additional analyses:

We plan to repeat the above described primary analyses in the following pre-defined baseline subgroups

- SBP <90 mm Hg *versus* SBP ≥ 90 mm Hg
- Lactate <2 mmol/L *versus* ≥ 2.0 mmol/L
- SBP <90 mm Hg after 1000ml of fluid administered in less than 60 minutes and lactate ≥2.0 mmol/L and first dose of intravenous antimicrobials commenced *versus* patients not meeting all three inclusion criteria
- Source of sepsis (respiratory *versus* other; abdominal source *versus* other)
- Age (<65 *versus* ≥65 years)
- Severity of illness (e.g. quartiles of APACHE score)
- Co-morbidities (presence *versus* absence of cardiovascular disease)
- Hospital type (Metropolitan, Urban District, Regional, Rural)

A formal sample size calculation will not be performed as this is a descriptive study. However, it is anticipated that comprehensive data on over 400 patients meeting the study entry criteria will be collected. With a minimum of 400 patients, this study will be able to identify point estimates for proportions with a 95% confidence interval of less than +/- 5%.

DISCUSSION

The question of fluid volume in sepsis resuscitation has been identified as one of the top research questions by leading sepsis experts from around the world.[1] Among patients with sepsis in the ICU, evidence supports a fluid-sparing strategy.[19] However, there is a

paucity of data to guide practice during the initial resuscitation phase in ED. Clinical trials from low-income settings have found harm associated with the use of fluid boluses during initial resuscitation,[12,14] but differences in populations and healthcare settings prevent translation of these results to high-income countries.

Sepsis mortality in Australia and New Zealand has declined in the past two decades.[20] It remains unclear to what degree fluid resuscitation with haemodynamic targets is responsible for this reduction in mortality. In practice, patients vary in their requirement for, and responsiveness to, IV fluid resuscitation. Clinicians typically assess the response to initial titrated fluid boluses and subsequently commence a vasopressor infusion should features of hypotension or hypoperfusion persist despite 'optimal' fluid resuscitation. An alternative approach is to introduce a vasopressor at an earlier stage as a 'fluid sparing' strategy.[21] A previous observational study of fluid and vasopressor practice in 32 Australian and New Zealand hospitals[22] predated the publication of the FEAST trial[12] and showed that 32% of patients received vasopressors in the first six hours after enrolment. Current practices outside the setting of a clinical trial are unknown, and the extent to which practice varies between a liberal fluid/later vasopressor strategy compared to one of a restricted volume/earlier vasopressor is uncertain.

Where equipoise exists, it is essential that definitive evidence be sought before implementing a change in practice. This is illustrated by the findings of a recent large multicentre clinical trial of a fluid-sparing strategy among high-risk surgical patients.[23] Contrary to expectations based upon previous smaller trials, the restricted strategy conferred no mortality benefit and was associated with a higher incidence of complications. This cautions against the early adoption of management strategies based upon a limited evidence-base and strengthens the rationale for a randomised trial for sepsis in an ED setting.[24]

There are several critical questions to be addressed before embarking on a clinical trial to evaluate differences in clinical outcomes with different resuscitation strategies among patients with septic shock. These are the incidence of patients meeting the trial criteria, their associated rate of mortality and the spectrum of usual practice. The clinical

heterogeneity of sepsis requires an individualised approach to resuscitation, so any trial needs to provide sufficient flexibility to be acceptable to clinicians, while ensuring there is sufficient separation in fluid volumes between the study groups to deliver a plausible treatment effect. Before starting a large-scale trial of a fluid volume-sparing resuscitation, it is essential that current practice and the extent of variation in usual care are defined, to establish a baseline and evaluate the scope for evaluating the planned intervention.

The ARISE FLUIDS observational study will provide high-level evidence to address key unresolved questions. It involves a large number of hospitals including tertiary, urban district as well as regional and remote facilities with a wide geographical spread. It will provide a 30-day snapshot of contemporary ED practice across varying levels of onsite ICU facilities. As such, ARISE FLUIDS will be the largest such study in our region, incorporating more than double the number of sites as the ARISE observational study in 2009.[24] In addition to providing a valuable dataset to inform a future clinical trial, the study will provide important insights into screening procedures and potential barriers to recruitment. More generally, this study will build research capacity for multicentre research and strengthen collaborations between the disciplines of emergency medicine and intensive care.

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CONFLICTS OF INTEREST

Gerben Keijzers, Stephen Macdonald are section editors for *Emergency Medicine Australasia*.

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List of participating institutions for ARISE FLUIDS observational study

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New Zealand (10):

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Queensland (18):

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Tasmania (2):

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Victoria (12):

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Western Australia (9):

Albany Regional Hospital, Armadale-Kelmscott District Memorial Hospital, Broome Hospital, Bunbury Regional Hospital, Fiona Stanley Hospital, Nickol Bay Hospital, Midland St John of God Hospital, Rockingham General Hospital, Royal Perth Hospital

Table 1

Baseline participant characteristics

Variables	
Age (years)	
Male Sex N (%)	
Weight (kg)	
Temperature ^{o}C	
Heart rate (beats/minute)	
Respiratory rate (breaths/minute)	
Mean arterial pressure (mm Hg)	
FiO_2	
SpO_2 (%)	
GCS	
Lactate (mmol/L)	
APACHE II score	
Time from triage to T0 (hours)	
Time from triage to first IV antimicrobials (minutes)	
Total fluid volume prior to T0 (ml)	
Prior living status	

Data are median (interquartile range) or mean +/- standard deviation, or as stated.
(T0 is defined as the time when all 3 inclusion criteria have been met)

Table 2 Process of care and clinical outcomes at 6 and 24 hours post-recruitment

Process of care variable	**Outcome variables**
Total cumulative fluid volumes - Between T0-T6 - Between T0-T24 - Prior to commencing vasopressor	Mortality - In-hospital mortality - ICU mortality - 28-day mortality
Types (and volume) of each fluid administered	Infection - Source of infection - Source control procedures
In patients receiving vasopressors: - Route - Duration - Timing - Type of vasopressor	ED outcomes - Disposition from ED - ED length of stay (mins)
Vital signs Haemodynamic monitoring	ICU outcomes - Proportion admitted to ICU (within 24 hours of ED presentation) - ICU duration of stay (hours) - Proportion receiving vasopressors - Duration of vasopressor support - Proportion receiving invasive ventilation - Duration of ventilation (hours) - Proportion of receiving acute renal replacement therapy (RRT) - Duration of RRT (hours)
Blood gas analyses, biochemistry and haematology results, including lactate	Hospital outcomes - Hospital length of stay - Destination on discharge for survivors (home *versus* care facility)

Data are median (interquartile range) or mean +/- standard deviation, or as stated. ED, emergency department; ICU, intensive care unit; RRT, renal replacement therapy

Figure 1 Proposed participant flowchart